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Review Article

Oxidative stress, inflammation, and cancer: How are they linked?

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ABSTRACT

Extensive research during the past 2 decades has revealed the mechanism by which continued oxidative stress can lead to chronic inflammation, which in turn could mediate most chronic diseases including cancer, diabetes, and cardiovascular, neurological, and pulmonary diseases. Oxidative stress can activate a variety of transcription factors including NF-κB, AP-1, p53, HIF-1α, PPAR-γ, β-catenin/Wnt, and Nrf2. Activation of these transcription factors can lead to the expression of over 500 different genes, including those for growth factors, inflammatory cytokines, chemokines, cell cycle regulatory molecules, and anti-inflammatory molecules. How oxidative stress activates inflammatory pathways leading to transformation of a normal cell to tumor cell, tumor cell survival, proliferation, chemoresistance, radioresistance, invasion, angiogenesis, and stem cell survival is the focus of this review. Overall, observations to date suggest that oxidative stress, chronic inflammation, and cancer are closely linked.

Contents

Introduction . . . 1604
Inflammatory network . . . 1604
Pro-oxidant network . . . 1605
Cellular transformation . . . 1606
Tumor cell survival . . . 1607
Tumor cell proliferation . . . 1607
Tumor cell invasion . . . 1608
Tumor cell angiogenesis . . . 1608
Chemoresistance . . . 1609
Radioresistance . . . 1610
Stem cell survival . . . 1610
Stromal cell signaling . . . 1611
Conclusion . . . 1611
Acknowledgments . . . 1611
References . . . 1611

Abbreviations: Akt, AKT8 virus oncogene cellular homolog; AP-1, activator protein-1; Cdk, cyclin-dependent kinase; CSC, cancer stem cell; Cu-ZnSOD, copper–zinc superoxide dismutase; CXCR4, CXC chemokine receptor 4; EC-SOD, extracellular superoxide dismutase; eNOS, endothelial nitric oxide synthase; ERK/MAPK, extracellular signal-regulated kinase/mitogen-activated protein kinase; FGF, fibroblast growth factor; Flk1/KDR, fetal liver kinase 1/kinase insert domain receptor; GPx, glutathione peroxidase; GSH, glutathione; HIF-1α, hypoxia-inducible factor-1α; HMOX-1, heme oxygenase-1; ICAM-1, intercellular adhesion molecule-1; IκBα, inhibitor of κBα; IL, interleukin; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinase; c-Jun, cellular Ju-nanna; Keap1, Kelch-like ECH-associated protein 1; LPS, lipopolysaccharide; MDR, multidrug resistance; MDM2, murine double minute 2; MKP, mitogen-activated protein kinase phosphatase; MMP, metalloproteinase; Mn-SOD, manganese superoxide dismutase; Myc, avian myeloblastosis virus oncogene; NF-κB, nuclear factor κB; nNOS, neuronal NOS; Nox, NADPH oxidase; Nrf2, NF-E2 related factor-2; 8-OHdG, 8-hydroxydeoxyguanosine; PGP, P-glycoprotein; PI3K, phosphoinositide 3-kinase; PPAR-γ, peroxisome proliferator-activated receptor-γ; PTEN, phosphatase and tensin homolog deleted from chromosome 10; Prx, peroxiredoxin; Ras, rat sarcoma viral oncogene; ROS, reactive oxygen species; RNS, reactive nitrogen species; SOD, superoxide dismutase; STAT3, signal transducer and activator of transcription 3; TAM, tumor-associated macrophages; TGF-β, transforming growth factor-β; TLR, toll-like receptor; TNF, tumor necrosis factor; TSP-1, thrombospondin-1; VEGF-A, vascular endothelial growth factor-A; Wnt, wint.

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Introduction

Oxidative stress is defined as an imbalance between production of free radicals and reactive metabolites, so-called oxidants or reactive oxygen species (ROS), and their elimination by protective mechanisms, referred to as antioxidants. This imbalance leads to damage of important biomolecules and cells, with potential impact on the whole organism [1]. ROS are products of a normal cellular metabolism and play vital roles in the stimulation of signaling pathways in plant and animal cells in response to changes in intra- and extracellular environmental conditions [2]. Most ROS are generated in cells by the mitochondrial respiratory chain [3]. During endogenous metabolic reactions, aerobic cells produce ROS such as superoxide anion (O_2^{-}), hydrogen peroxide (H_2O_2), hydroxyl radical ($OH^{\bullet}$), and organic peroxides as normal products of the biological reduction of molecular oxygen [4]. The electron transfer to molecular oxygen occurs at the level of the respiratory chain, and the electron transport chains are located in the membranes of the mitochondria [5,6]. Under hypoxic conditions, the mitochondrial respiratory chain also produces nitric oxide (NO), which can generate reactive nitrogen species (RNS) [3]. RNS can further generate other reactive species, e.g., reactive aldehydes—malondialdehyde and 4-hydroxynonenal—by inducing excessive lipid peroxidation [7]. Proteins and lipids are also significant targets for oxidative attack, and modification of these molecules can increase the risk of mutagenesis [8].

Under a sustained environmental stress, ROS are produced over a long time, and thus significant damage may occur to cell structure and functions and may induce somatic mutations and neoplastic transformation [9,10]. Indeed, cancer initiation and progression have been linked to oxidative stress by increasing DNA mutations or inducing DNA damage, genome instability, and cell proliferation [11].

The skin, for example, is chronically exposed to both endogenous and environmental pro-oxidants because of its interface function between the body and the environment, and to protect the skin against this overload of oxidant species, it needs a well-organized system of both chemical and enzymatic antioxidants [12]. The lungs, which are directly exposed to oxygen concentrations higher than in most other tissues, are protected against these oxidants by a variety of antioxidant mechanisms [13]. Furthermore, aging, which is considered an impairment of body functions over time, caused by the accumulation of molecular damage in DNA, proteins, and lipids, is also characterized by an increase in intracellular oxidative stress due to the progressive decrease in intracellular ROS scavenging [14]. Acting to protect the organism against these harmful pro-oxidants is a complex system of enzymatic antioxidants (e.g., superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase, catalase) and nonenzymatic antioxidants (e.g., glutathione (GSH), vitamins C and D) [15] (Fig. 1).

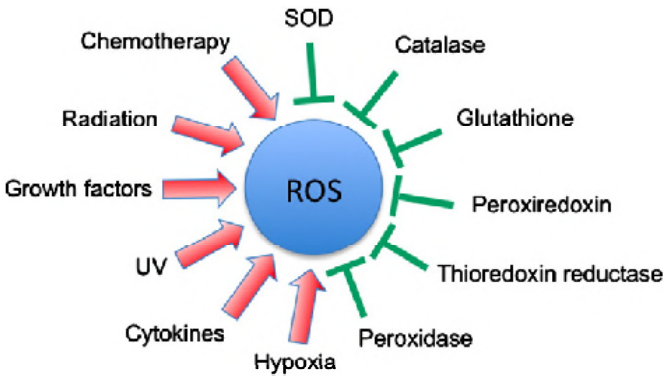

Fig. 1. Schematic representation of various activators and inhibitors of reactive oxygen species production.

ROS are involved in a wide spectrum of diseases, including chronic inflammation (Table 1), and in a wide variety of cancers (Table 2).

Chronic inflammation is induced by biological, chemical, and physical factors and is in turn associated with an increased risk of several human cancers [54]. The link between inflammation and cancer has been suggested by epidemiological and experimental data [55,56] and confirmed by anti-inflammatory therapies that show efficacy in cancer prevention and treatment [57]. The fact that continuous irritation over long periods of time can lead to cancer had already been described in the traditional Ayurvedic (meaning "the science of long life") medical system, written as far back as 5000 years ago [58]. Whether this irritation is the same as what Rudolf Virchow referred to as inflammation in the 19th century is uncertain [59]. Virchow first noted that inflammatory cells are present within tumors and that tumors arise at sites of chronic inflammation [60]. This inflammation is now regarded as a "secret killer" for diseases such as cancer. For example, inflammatory bowel diseases such as Crohn disease and ulcerative colitis are associated with increased risk of colon adenocarcinoma [61–63], and chronic pancreatitis is related to an increased rate of pancreatic cancer [64].

The exact mechanisms by which a wound-healing process turns into cancer are topics of intense research [57,65], and possible mechanisms include induction of genomic instability, alterations in epigenetic events and subsequent inappropriate gene expression, enhanced proliferation of initiated cells, resistance to apoptosis, aggressive tumor neovascularization, invasion through tumor-associated basement membrane, and metastasis [66]. How oxidative stress modulates these different stages of inflammation-induced carcinogenesis is the focus of this review.

Inflammatory network

The sources of inflammation are widespread and include microbial and viral infections; exposure to allergens, radiation, and toxic chemicals; autoimmune and chronic diseases; obesity; consumption of alcohol; tobacco use; and a high-calorie diet [60,67]. In general, the longer the inflammation persists, the higher the risk of cancer. Two stages of inflammation exist, acute and chronic inflammation. Acute inflammation is an initial stage of inflammation (innate immunity), which is mediated through the activation of the immune system. This type of inflammation persists only for a short time and is usually beneficial for the host. If the inflammation lasts for a longer period of time, the second stage of inflammation, or chronic inflammation, sets in and may predispose the host to various chronic illnesses, including cancer [68]. During inflammation, mast cells and leukocytes are recruited to the site of damage, which leads to a "respiratory burst"

Table 1
A partial list of diseases that have been linked to reactive oxygen species

Disease	Reference
Acute respiratory distress syndrome	[16]
Aging	[17]
Alzheimer	[18,19]
Atherosclerosis	[20]
Cancer	[21–23]
Cardiovascular disease	[24,25]
Diabetes	[26]
Inflammation	[27]
Inflammatory joint disease	[28]
Neurological disease	[29]
Obesity	[30,31]
Parkinson	[32,33]
Pulmonary fibrosis	[34,35]
Rheumatoid arthritis	[36]
Vascular disease	[37,38]

Table 2
A partial list of cancers that have been linked to reactive oxygen species

Cancer	Reference
Bladder	[39]
Brain tumor	[40]
Breast	[41]
Cervical	[42]
Gastric (stomach)	[43]
Liver	[44]
Lung	[45]
Melanoma	[46]
Multiple myeloma	[47]
Leukemia	[48]
Lymphoma	[49]
Oral	[50]
Ovarian	[51]
Pancreatic	[52]
Prostate	[10]
Sarcoma	[53]

due to an increased uptake of oxygen and, thus, an increased release and accumulation of ROS at the site of damage [7,65].

On the other hand, inflammatory cells also produce soluble mediators, such as metabolites of arachidonic acid, cytokines, and chemokines, which act by further recruiting inflammatory cells to the site of damage and producing more reactive species. These key mediators can activate signal transduction cascades as well as inducing changes in transcription factors, such as nuclear factor κB (NF-κB), signal transducer and activator of transcription 3 (STAT3), hypoxia-inducible factor-1α (HIF-1α), activator protein-1 (AP-1), nuclear factor of activated T cells, and NF-E2 related factor-2 (Nrf2), which mediate immediate cellular stress responses (Fig. 2). Induction of cyclo-oxygenase-2 and inducible nitric oxide synthase (iNOS), aberrant expression of inflammatory cytokines (tumor necrosis factor (TNF), interleukin-1 (IL-1), IL-6) and chemokines (IL-8, CXC chemokine receptor 4 (CXCR4)), as well as alterations in the expression of specific microRNAs have also been reported to play a role in oxidative stress-induced inflammation [69]. This sustained inflammatory/oxidative environment leads to a vicious circle, which can damage healthy neighboring epithelial and stromal cells and over a long period of time may lead to carcinogenesis [70].

As an example, mutations in the rat sarcoma viral oncogene (Ras) induce an inflammatory response. Ras, which is mutated in approximately 25% of all malignancies [71], promotes cell proliferation, tumor growth, and angiogenesis of malignant cells. During inflammatory stimuli, Ras induces the expression of various inflammatory gene products, including the proinflammatory cytokines IL-1, IL-6, and IL-11 and the chemokine IL-8 [72].

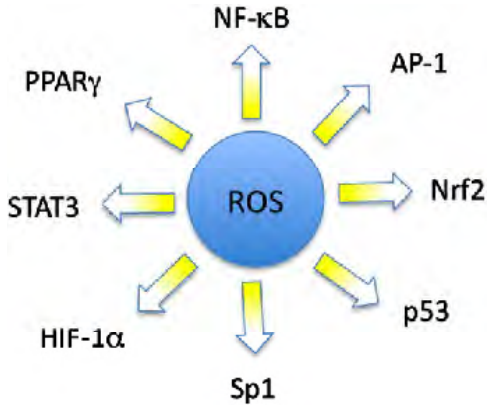

Fig. 2. Schematic representation of various transcription factors that are modulated by reactive oxygen species.

Pro-oxidant network

After an inflammatory stimulus, initiation of carcinogenesis mediated by ROS may be direct (oxidation, nitration, halogenation of nuclear DNA, RNA, and lipids) or mediated by the signaling pathways activated by ROS. With the help of the mitochondrial respiratory chain, aerobic organisms are able to attain a far greater energy production efficiency compared with anaerobic organisms. However, one disadvantage of aerobic respiration is continuous electron leakage to O_2 during mitochondrial ATP synthesis. In fact, 1–5% of total oxygen consumed in aerobic metabolism gives rise to O_2^-, an example of ROS. To protect against this free radical, the main enzyme for its degradation, the manganese superoxide dismutase (Mn-SOD), dismutates it into H_2O_2 and water [73].

H_2O_2, another example of ROS, may be formed either by dismutation from superoxide anion or spontaneously in peroxisomes from molecular oxygen [74–76]. Despite its lesser reactivity compared with other ROS, H_2O_2 plays an important role in carcinogenesis because it is capable of diffusing throughout the mitochondria and across cell membranes and producing many types of cellular injury [74,75]. The main injurious effects of ROS in mammalian cells are, however, mediated by $^{\bullet}OH$. It has a very unstable electron structure and is therefore unable to diffuse more than one or two molecular diameters before it reacts in practice with any cellular component [76,77]. The majority of $^{\bullet}OH$ in vivo is produced in the presence of reduced transition metals (ions of Fe, Cu, Co, or Ni), mainly via the Fenton reaction when Fe^{2+} contacts H_2O_2. The $^{\bullet}OH$-derived DNA damage includes the generation of 8-hydroxyguanosine, the hydrolysis product of which is 8-hydroxydeoxyguanosine (8-OHdG). 8-OHdG is the most widely used fingerprint of radical attack on DNA [77,78]. 8-OHdG has been strongly implicated in carcinogenesis progression. For example, in breast carcinomas, 8-OHdG has been reported to be increased 8- to 17-fold in breast primary tumors compared with nonmalignant breast tissue [79–81].

$NO^{\bullet}$, another free radical implicated in carcinogenesis, is a short-lived free radical generated from l-arginine [82] that is effective against pathogens. The major part of $NO^{\bullet}$ is synthesized by iNOS, usually after challenge by immunological or inflammatory stimuli [82,83]. NO is synthesized from l-arginine by the enzyme nitric oxide synthase (NOS). The constitutive (calcium-dependent) isoforms, neuronal NOS (nNOS or bNOS) and endothelial NOS (eNOS), produce small amounts of NO, which acts as a neurotransmitter and vasodilator, respectively [84]. The inducible (calcium-independent) isoform, iNOS, produces much larger amounts of NO and is expressed only during inflammation. Whereas iNOS can produce injurious amounts of RNS, eNOS and nNOS produce beneficial amounts under physiological conditions [85]. iNOS is induced by cytokines such as interferon-γ, TNF-α, IL-1, and lipopolysaccharide (LPS). LPS activation induces the translocation of NF-κB, from the cytoplasm to the nucleus, where it interacts with κB elements in the NOS2 (iNOS) 5′ flanking region, triggering NOS2 transcription [86].

Defective autophagy of old mitochondria (mitophagy) can also be a major source of ROS [87]. These ROS produced by damaged mitochondria can promote tumor development, probably by perturbing the signal transduction adaptor function of p62-controlling pathways [88].

To control the balance between production and removal of ROS (Fig. 3), a variety of DNA repair enzymes exist, although antioxidants are more specific and efficient in protecting cells from radicals. This antioxidant system includes both endogenous and exogenous and enzymatic and nonenzymatic antioxidants. GSH is a tripeptide and the major endogenous antioxidant produced by cells and helps to protect cells from ROS such as free radicals and peroxides [89]. It is now well established that ROS and electrophilic chemicals can damage DNA and that GSH can protect against this type of damage [90]. GSH can also directly detoxify carcinogens through phase II metabolism and

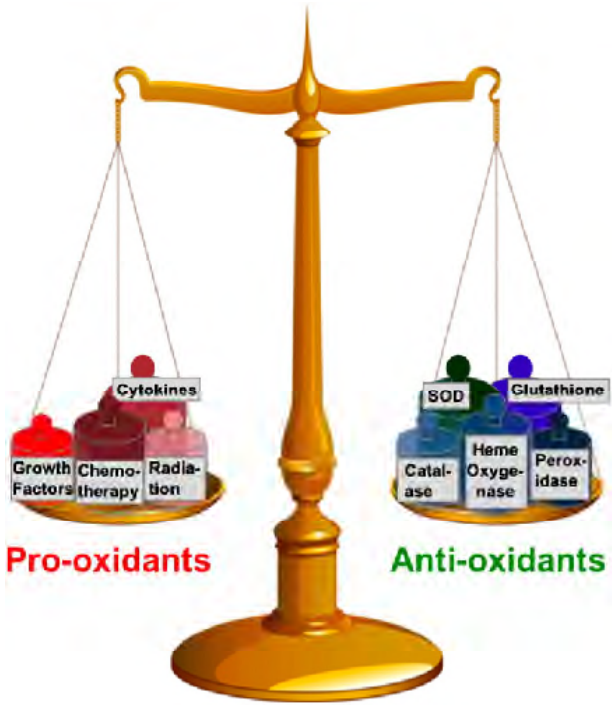

Fig. 3. Model of a balance between pro-oxidants and antioxidants. Under normal conditions, antioxidants outbalance pro-oxidants, but under oxidative conditions, pro-oxidants prevail over antioxidants, which can lead to many inflammatory diseases, including cancer.

subsequent export of these chemicals from the cell. On the other hand, elevated GSH levels are observed in various types of cancerous cells and solid tumors, and this tends to make these cells and tissues more resistant to chemotherapy [91–93].

SODs were the first characterized antioxidant enzymes [94]. Three types of SOD are expressed in human cells, copper–zinc SOD (Cu-ZnSOD), Mn-SOD, and extracellular-SOD (EC-SOD), all of which are able to dismutate two $O_2^{\bullet-}$ anions to H_2O_2 and molecular oxygen. Catalase is then responsible for detoxification of H_2O_2 to water. The GPx's are another group of enzymes capable of reducing hydroperoxides, including lipid hydroperoxides, using GSH as substrate. The oxidized form of glutathione disulfide is again reduced by the specific enzyme glutathione reductase. Peroxiredoxins (Prx's) were first described 20 years ago, and as for catalase and GPx, the main function of peroxiredoxins is to reduce alkyl hydroperoxides and H_2O_2 to the corresponding alcohol or water.

Direct effects of ROS, generally attributed to high concentrations at the site of damage, include DNA strand breaks, point mutations, aberrant DNA cross-linking, and mutations in proto-oncogenes and tumor-suppressor genes, thus promoting neoplastic transformation [7,95]. For example, ROS can reduce the expression and enzymatic activity of the DNA mismatch repair genes mutS homologs 2 and 6 and can increase the expression of DNA methyltransferases, leading to a global hypermethylation of the genome [60]. This leads to promoter silencing of several genes, such as adenomatous polyposis coli, cyclin-dependent kinase inhibitor-2, breast cancer susceptibility gene 1, retinoblastoma protein, murine double minute 2 (MDM2), and the DNA mismatch repair gene, human mutL homolog 1 [96,97].

On the other hand, low or transient levels of ROS can activate cellular proliferation or survival signaling pathways, such as the NF-κB, AP-1, extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK), and phosphoinositide 3-kinase/Akt8 virus oncogene cellular homolog (PI3K/Akt) pathways (Table 3).

For example, H_2O_2 is able to degrade IκBα, the inhibitory subunit of NF-κB [137]. Protein kinase C, which participates in a variety of pathways regulating transcription and cell cycle control, is also activated by H_2O_2 [137]. In addition, ROS induce both the activation and synthesis of AP-1, a regulator of cell growth, proliferation, and apoptosis [138,139], and transcription factors such as STAT3, HIF-1α, and p53 [118,140,141].

Table 3
A partial list of signaling pathways linked to reactive oxygen species

Signaling intermediate	Reference
AHR	[98]
AP-1	[99,100]
ATM	[101]
cAMP	[102]
cAMP-dependent protein kinase A	[103]
Cdk5	[104]
Chemokine	[70]
c-Myc	[99]
CREB	[103]
Cyclins and cell cycle regulation	[105]
Cytokine network	[66]
DNA methylation	[106]
DNA repair mechanism	[107]
Epidermal growth factor	[108]
eNOS	[109]
ERK	[110]
Fas	[111]
FOXO	[112]
HIF-1α	[113]
Heme oxygenase-1	[114]
IL-10	[115]
iNOS	[109]
Integrin	[116]
Interferon	[117]
JAK/STAT	[118]
JNK	[119]
MAPK	[110]
Mismatch repair	[120]
mTor	[121]
NAD(P)H quinone oxidoreductase 1	[122]
NF-κB	[123]
Nrf2	[124]
PI3K/Akt	[125]
p38	[126]
p53	[127,128]
Protein kinase C	[129]
PPAR-γ	[130]
PTEN	[131]
Protein tyrosine phosphatases/Protein tyrosine kinases (PTPs/PTKs)	[132]
Sp1	[133]
TNF	[5]
VEGF	[134]
Wnt	[135,136]

Cellular transformation

Chronic inflammation has been linked to various steps involved in carcinogenesis, including cellular transformation, promotion, survival, proliferation, invasion, angiogenesis, and metastasis [65,142]. How oxidative stress is involved in these various steps is discussed in the following sections.

Cancer is a multistage process defined by at least three stages: initiation, promotion, and progression [143–145]. Oxidative stress interacts with all three stages of this process. During the initiation stage, ROS may produce DNA damage by introducing gene mutations and structural alterations into the DNA. In the promotion stage, ROS can contribute to abnormal gene expression, blockage of cell-to-cell communication, and modification of second-messenger systems, thus resulting in an increase in cell proliferation or a decrease in apoptosis of the initiated cell population. Finally, oxidative stress may also participate in the progression stage of the cancer process by adding further DNA alterations to the initiated cell population [146].

In recent years, considerable evidence has demonstrated that ROS are involved in the link between chronic inflammation and cancer [147–149]. Indeed, an important characteristic of tumor promoters is their ability to recruit inflammatory cells and to stimulate them to generate ROS [150,151]. Tumor promotion, for example, can be inhibited in animal models by the use of agents, including certain antioxidants as well as steroids and retinoids, that can inhibit the phagocyte respiratory burst [148,150]. Moreover, increased levels of oxidatively modified DNA bases (such as thymidine glycol, 5-hydroxymethyl-2′-deoxyuridine, and 8-OHdG) have been induced in the skin of mice by topical phorbol 12-myristate 13-acetate exposure [152]. 8-OHdG has also been identified in the epidermis of nude mice exposed to near-UV [153]. In addition, genetic damage and neoplastic transformation have been demonstrated in cells cocultured in vitro with activated phagocytes [149], and the genotoxic effects observed include formation of DNA strand breaks [151], sister chromatid exchange [154], and mutations [155]. Furthermore, the DNA base modifications observed are characteristic of an attack by the reactive oxygen species $^{\bullet}OH$ [156]. Inflammatory cells may also increase DNA damage by activating procarcinogens to become DNA-damaging species; for example, neutrophils can activate aromatic amines, aflatoxins, estrogens, phenols, and polycyclic aromatic hydrocarbons by ROS-dependent mechanisms [148,157]. On the other hand, both neutrophils and macrophages have themselves been shown to release large quantities of superoxide, hydrogen peroxide, and hydroxyl radical after activation of their redox metabolism [158].

In fact, initial experiments on the role of ROS in tumor initiation have assumed that oxidative stress acts as a DNA-damaging agent, effectively increasing the mutation rate within cells and thus promoting oncogenic transformation [159]. However, more recent studies have revealed that in addition to inducing genomic instability, ROS can specifically activate certain signaling pathways and thus contribute to tumor development through the regulation of cellular proliferation, angiogenesis, and metastasis [160]. For example, nitrosative stress has been shown to play a critical role in inflammation-associated carcinogenesis by activating AP-1, a representative redox-sensitive transcription factor [161], which is involved in cell transformation and proliferation [139,162].

Tumor cell survival

One of the key characteristics of tumor cells is their increased ability to survive compared with normal cells. ROS are reported to be tumorigenic by virtue of their ability to increase cell proliferation, survival, and cellular migration. ROS can induce DNA damage, leading to genetic lesions that initiate tumorigenicity and subsequent tumor progression. On the other hand, ROS can also induce cellular senescence and cell death and can therefore function as antitumorigenic agents. Whether ROS promote tumor cell survival or act as antitumorigenic agents depends on the cell and tissues, the location of ROS production, and the concentration of individual ROS.

ROS have been reported to play a major role in tumor initiation and survival induced by a variety of agents in both animal models and humans [158,163,164] by mediating cellular signal transduction pathways. These signaling pathways are involved in the transmission of inter- or intracellular information and are critical for supporting tumor cell survival and establishing cell fate. The reduced nicotinamide adenine dinucleotide phosphate oxidase (Nox) family of enzymes, one of the potential sources of ROS production, has been reported to promote tumor cell survival and growth [165]. For example, Nox4 and Nox5 promote tumor cell survival in pancreatic and lung cancers, respectively [165]. The serine–threonine kinase Akt has been reported to down-regulate antioxidant defenses and promote tumor cell survival [166]. ROS have also been reported to activate Akt by inhibiting phosphatase and tensin homolog deleted from chromosome 10 (PTEN), the phosphatase counteracting PI3K-dependent Akt activation [167]. Akt may foster tumorigenesis by multiple means [168,169], for example, by stabilizing cellular avian myeloblastosis virus oncogene (c-Myc) and cyclin D1 or by inducing degradation of the cyclin-dependent kinase (Cdk) inhibitor, p27 kinase inhibitor protein. Akt is also a profound inhibitor of apoptosis because of its ability to inactivate proapoptotic molecules, including caspase-9 and the Bcl-2 homology 3-only protein Bcl-XL/Bcl-2-associated death promoter, and by triggering the activity of the transcription factor NF-κB. In addition, Akt promotes nuclear translocation of the ubiquitin ligase MDM2, which counteracts p53-mediated apoptosis. An important aspect of Akt's promotion of cell survival involves alterations in cellular energy metabolism [168,169]. Thus, by preventing apoptosis and increasing oxidative metabolism, Akt lies at the hub of complex signaling networks that integrate a multitude of potentially oncogenic signals.

Tumor cell proliferation

Uncontrolled tumor cell proliferation requires the up-regulation of multiple intracellular signaling pathways, including cascades involved in survival, proliferation, and cell cycle progression. The most significant effects of oxidants on signaling pathways have been observed in the MAPK/AP-1 and NF-κB pathways [170]. The induction of redox-sensitive pathways during tumor cell proliferation is necessary because cell division presents tremendous energy requirements and the production of metabolites from energy-generating reactions must be buffered to prevent oxidative damage and ultimately cell death [171].

Of the MAPK family, which modulates gene expression through phosphorylation of a wide array of transcription factors, the ERK pathway is the most commonly linked with the regulation of cell proliferation. Activation of the ERK, c-Jun N-terminal kinase (JNK), and p38 subfamilies has been observed in response to changes in the cellular redox balance [172]. The induction of AP-1 by H_2O_2, cytokines, and other stressors, for example, is mediated mainly by JNK and p38 MAPK cascades [173]. Once activated, JNK proteins translocate to the nucleus and phosphorylate c-Jun and activating transcription factor-2, enhancing transcriptional activities [174,175]. H_2O_2 can activate MAPKs and thereby AP-1 in several manners.

Redox status has also been shown to have an impact on NF-κB regulation. NF-κB regulates several genes involved in cell transformation, proliferation, and angiogenesis [176]. Carcinogens and tumor promoters, including UV radiation, phorbol esters, asbestos, alcohol,and benzo(a)pyrene, are among the external stimuli that activate NF-κB [177,178]. Expression of NF-κB has been shown to promote cell proliferation, whereas inhibition of NF-κB activation blocks cell proliferation [179]. Additionally, tumor cells from blood neoplasms, and cell lines from various cancers, including colon, breast, pancreas, and squamous cell carcinoma, have all been reported to constitutively express activated NF-κB [180]. The mechanism for activation of NF-κB by ROS is not clear, and the relationship between NF-κB and ROS is complex [123]. Although mild oxidative stress can lead to modest NF-κB activation, extensive oxidative stress can inhibit NF-κB [123]. Furthermore, NF-κB can protect cells from oxidative stress through induction of the ferritin heavy chain and SOD2 genes, which are both regulated by NF-κB [181,182]. On the other hand, ROS are believed to be implicated as second messengers involved in the activation of NF-κB via TNF and IL-1 [183] and indeed, suppression of TNF and IL-1 was shown to down-regulate the expression of active NF-κB and inhibit proliferation of lymphoma and myelogenous leukemia cells [184]. The importance of ROS in NF-κB activation is further supported by studies demonstrating that activation of NF-κB by nearly all stimuli can be blocked by antioxidants, such as l-cysteine, N-acetylcysteine, thiols, green tea polyphenols, and vitamin E [185,186], although this might be not very specific because antioxidants have multiple targets [187]. Likewise, NF-

κB activity was increased in cells that overexpressed SOD and decreased in cells overexpressing catalase [188].

Kinases, such as protein kinase C, can also be activated by H_2O_2 and redox cycling quinones [189,190]. Similarly, H_2O_2 leads to the activation of protein kinase B/Akt, which is associated with heat shock protein 27 [191].

That ROS such as H_2O_2 and superoxide anion induce mitogenesis and cell proliferation has now been demonstrated in several mammalian cell types [192]; and a reduction in cellular oxidants via supplementation with antioxidants such as superoxide dismutase, catalase, β-carotene, and flavonoids inhibits cell proliferation in vitro [193]. However, paradoxically high concentrations of ROS can trigger apoptotic or necrotic cell death [194–196].

Tumor cell invasion

Oxygen radicals may augment tumor invasion and metastasis by increasing the rates of cell migration. During transformation into invasive carcinoma, epithelial cells undergo profound alterations in morphology and adhesive mode, resulting in a loss of normal epithelial polarization and differentiation and a switch to a more motile, invasive phenotype. For example, treatment of mammalian carcinoma cells with hydrogen peroxide before intravenous injection into mice enhances lung metastasis formation, indicating that an important function for ROS is the seeding of metastatic tumor cells [197]. This might be due to a decreased attachment of tumor cells to the basal lamina or alternatively be due to the increased activity or expression of proteins that regulate cellular motility. For instance, oxidative stress regulates the expression of intercellular adhesion protein-1 (ICAM-1), a cell surface protein in endothelial and epithelial cells, most likely because of the activation of NF-κB. ICAM-1 together with IL-8 regulates the transendothelial migration of neutrophils and has a potential function in tumor metastasis [198].

On the other hand, it is believed that the matrix metalloproteinases (MMPs) play the central role, and their increased expression reportedly is associated with the invasion and metastasis of malignant tumors of various histogenetic origins [199]. For example, Mori et al. found that MMP-13, MMP-3, and MMP-10 were remarkably up-regulated by the oxidant directly, and their activities were critically implicated in the invasive potential induced in NMuMG cells in the reconstituted model [200]. Another subgroup of MMPs, gelatinases (MMP-2 and -9), which are key enzymes for degrading type IV collagen and are thought to play a critical role in tumor invasion and metastasis [199], were also found to be activated posttranscriptionally by prolonged oxidative treatment. These effector molecules activated under prolonged oxidative stress relate chronic inflammation to malignant transformation, in particular to the invasive potential of cells, at least at a molecular level.

MMPs are capable of cleaving most components of the basement membrane and extracellular matrix [201]. The activation of MMPs, such as MMP-2, probably occurs by the reaction of ROS with thiol groups in the protease catalytic domain [202]. In addition to their role as key regulators of MMP activation, ROS have been implicated in MMP gene expression [203]. Both hydrogen peroxide and nitric oxide donors, as well as the increased expression of iNOS, stimulate the expression of several MMPs (MMP-1, MMP-3, MMP-9, MMP-10, MMP-13) [203]. In fibroblastic cells, the sustained production of H_2O_2 recently was shown to activate MMP-2 and to increase cell invasion [204]. Oxidative stress may also modulate MMP expression by activation of Ras, or direct activation of the MAPK family members ERK1/2, p38, and JNK, or inactivation of phosphatases that regulate these proteins [160].

In addition, several studies have reported the involvement of chemokines and chemokine receptors in the invasion and metastasis of various types of tumors [205–208]. The metastatic potential of chemokines is attributed to their ability to induce the expression of MMPs, which facilitate tumor invasion [208,209]. Moreover, silencing of endogenous CXCR4 gene expression by CXCR4 short hairpin RNA inhibited the proliferation, adhesion, chemotaxis, and invasion of mucoepidermoid carcinoma cells [210]. In addition, recent data point to a role for the small guanosine triphosphatase Rac1 in motility and invasion of tumor cells in vitro by altering cell–cell and cell–matrix adhesion. For example, Rac1 activity induces ROS production in endothelial cells. These ROS can mediate Rac1-induced loss of cell–cell adhesion in primary human endothelial cells and thus might loosen the integrity of the endothelium [211].

It is becoming clear that a number of steps in the metastatic cascade, such as invasion, intravasation, and extravasation, are regulated by redox signaling [212]. One such redox signaling molecule is the electrophilic cyclopentenone prostaglandin 15d-PGJ2 (15-deoxy-12,14-prostaglandin J2), an inflammatory molecule [213], which can affect redox signaling through the posttranslational modification of critical cysteine residues in proteins such as actin, vimentin, and tubulin [214,215]. The fact that 15d-PGJ2 can alter the cytoskeleton [212] coincides with decreased migration and increased focal-adhesion disassembly, which might have important implications in the inhibition of metastatic processes such as invasion, intravasation, and extravasation. These results suggest a role for redox signaling pathways, rather than direct cytoskeletal disruption, in the mechanism of 15d-PGJ2 in cancer cells.

Finally, Cheng et al. demonstrated that ROS enhance the transendothelial migration of melanoma cells during intravasation and that this mechanism could potentially be triggered by ultraviolet radiation through the increased expression of thioredoxin-interacting protein and inhibition of thioredoxin [216].

Tumor cell angiogenesis

Solid tumors induce an angiogenic response by the host blood vessels to form a new vascular network for the supply of nutrients and oxygen [217]. This neovascular response is partly responsible for tumor growth and metastatic spread [218,219]. Angiogenesis in tumors is controlled by the so-called “angiogenic switch,” which allows the transition from low invasive and poorly vascularized tumors to highly invasive and angiogenic tumors. To increase further in size, tumor cells express a set of molecules that initiate tumor vascularization.

A number of cellular stress factors, including hypoxia, nutrient deprivation, and ROS, are important stimuli of angiogenic signaling [220]. In addition, overexpression of Ras has been linked to vascularization of tumors [221]. Indeed, transformation by Ras stabilizes HIF-1α and up-regulates the transcription of vascular endothelial growth factor-A (VEGF-A). Moreover, chemical antioxidants inhibit the mitogenic activity of Ras, indicating that ROS participate directly in malignant transformation. Finally, ROS stabilize HIF-1α protein and induce production of angiogenic factors by tumor cells [222].

The HIF system plays a significant role in angiogenesis, and the molecular mechanisms of its regulation have recently been characterized. In addition, HIF-independent mechanisms that involve a number of other molecules and transcription factors such as NF-κB and p53 have been described. p53 may interact with the HIF system but may also have direct effects on angiogenesis regulators or interfere with translation mechanisms of angiogenesis factors.

One other major factor in angiogenesis is VEGF, which is produced by the cells to stimulate the growth of new blood vessels. VEGF induces angiogenesis by stimulating endothelial cell proliferation and migration primarily through the receptor tyrosine kinase VEGF receptor 2, fetal liver kinase 1/kinase insert domain receptor (Flk1/KDR). VEGF binding initiates tyrosine phosphorylation of KDR, which results in activation of downstream signaling enzymes including ERK1/2, Akt, and endothelial nitric oxide synthase (eNOS), which contribute to angiogenic-related responses in endothelial cells [134].

A number of oncogenes and tumor-suppressor genes that are normally associated with cell transformation (Ras, c-Myc, murine sarcoma 3611 oncogene, human epidermal growth factor receptor-2, c-Jun, and steroid receptor coactivator) regulate angiogenesis through up-regulation of VEGF or down-regulation of thrombospondin-1 (TSP-1), an angiogenesis suppressor [223,224]. Furthermore, mutated p53 up-regulates VEGF and, in contrast, wild-type p53 decreases VEGF production and increases TSP-1 [225]. Angiogenic factors such as VEGF, fibroblast growth factor (FGF), and platelet-derived growth factor are released into the tumor microenvironment by tumor or inflammatory cells in response to various stimuli, such as ROS [226]. The released growth factors activate endothelial cells that give rise to new blood vessels [227,228].

Monte et al. have demonstrated that lymphocyte-induced angiogenesis is triggered by ROS stimulation and that this response can be blocked by the administration of a free radical scavenger to tumor-bearing mice [229,230]. In addition, the administration of H_2O_2 or an oxidative stress-producing drug (doxorubicin) to normal mice activated in vivo angiogenesis [229].

Because of reduced physiological tissue oxygen tension (hypoxia), which occurs during tumor initiation, tumors often become hypoxic. Under hypoxic conditions, cells activate signaling pathways, which regulate proliferation, angiogenesis, and death. Cancer cells have adapted to these pathways, effectively allowing tumors to survive and even grow under adverse hypoxic conditions [160]. This adaptation of tumor cells to hypoxia contributes to the malignant phenotype and to aggressive tumor progression [231], and low oxygen tension in tumors is associated with increased metastasis and poor survival of patients with several forms of squamous tumor [232,233]. HIF-1α responds to these changes by specifically decreasing the oxygen (or hypoxia) level and up-regulating several genes to promote survival under low-oxygen conditions and thus promoting angiogenesis.

In conclusion, although previous sections indicate that all different substages of tumor development are affected by ROS and inflammation, early stages of cancer development (e.g., cellular transformation), involving DNA damage, are, however, most affected by ROS-generated inflammation. For example, colitis may develop into colon cancer after inflammatory infiltration, increased production of ROS, impairment of antioxidant defenses, DNA damage, and genetic and epigenetic alterations, resulting in the transformation of epithelial cells [234]. Or, bronchitis, which can lead to lung cancer, clearly links pro-oxidants, generated by cigarette smoke, to inflammation of the bronchus and eventually transformation of lung cells into lung cancer [235]. Similarly pancreatitis and esophagitis, both induced by tobacco and alcohol, may transform normal tissue into pancreatic or esophageal cancer if the antioxidant system is not sufficiently effective [236,237].

Chemoresistance

Despite many decades of research, the mechanisms underlying chemoresistance are still poorly understood. There is growing evidence that the inflammatory tumor microenvironment modulates not only cancer development but also cancer responsiveness and resistance to conventional anticancer therapies [238]. Experimental studies have led to the identification of various cancer cell-intrinsic resistance mechanisms, e.g., activation and/or overexpression of drug transporter proteins (e.g., P-glycoprotein), altered expression of detoxifying enzymes (e.g., glutathione S-transferase), or resistance to apoptosis/senescence pathways [239–242].

For example, an inflammatory response induces changes in the expression and activity of multidrug-resistance (MDR)-associated protein transporters, greatly affecting drug responses [243,244]. It has been shown that acute inflammation suppresses the drug transporter P-glycoprotein (PGP) in the liver, whereas it activates PGP in kidneys, resulting in changes in the pharmacokinetics of the PGP substrate doxorubicin [245]. Likewise, expression of MDR-associated protein 1 is elevated in inflamed intestine of patients with Crohn disease or ulcerative colitis [246]. Thus, enhanced states of inflammation influence proteins that are strongly linked with drug resistance.

In addition to the effects caused by inflammation, several chemotherapeutic agents have also been shown to activate the transcription factor NF-κB in human lung and cervical cancers and in T cells [247–249]. These agents are paclitaxel, vinblastine, vincristine, doxorubicin, daunomycin, 5-fluorouracil, cisplatin, and tamoxifen. Activation of NF-κB by these agents has been linked in turn with chemoresistance through serine phosphorylation of IκBα [250,251]. Various in vitro studies have supported a link between NF-κB activation, cytokine production, and chemoresistance. One pathway through which NF-κB can be activated is the Toll-like receptor (TLR) pathway. TLRs generally signal via the adapter protein myeloid differentiation primary response gene 88 leading to activation of NF-κB and production of proinflammatory cytokines. Activation of TLR signaling in ovarian cancer cell lines by exogenously added LPS resulted in an activated NF-κB pathway, which promoted secretion of proinflammatory cytokines and subsequently conferred resistance to paclitaxel [252,253]. Also, TNF receptor signaling promotes NF-κB activation and has been linked to chemoresistance. For example, exposure of breast cancer cells to exogenously added TNF-α results in selection for breast cancer cells that overexpress NF-κB, leading to increased cancer cell survival and resistance to ionizing radiation [254]. At the same time, cytokines produced by stromal cells in the tumor microenvironment (e.g., IL-1 or TNF-α) could potentially activate the NF-κB pathway in cancer cells and thus contribute to chemoresistance. These data call for functional in vivo studies to elucidate the involvement of the inflammatory tumor microenvironment in NF-κB-dependent chemoresistance.

Another mechanism that might be involved in chemoresistance is increased levels of GSH in cancer cells [92]. In particular, the overexpression of glutathione S-transferases (GSTs), the enzymes that catalyze the conjugation of reduced glutathione to electrophilic compounds [255], as well as efflux pumps may reduce the reactivity of various anticancer drugs [256]. The increase in the GST levels occurs by transcriptional activation mediated by Nrf2 [257]. Indeed, using genetic manipulation, Lau et al. have demonstrated a strong positive correlation between Nrf2 levels and resistance of three cancer cell lines to chemotherapeutic drugs such as cisplatin, doxorubicin, and etoposide [258]. Chemical activation of Nrf2 by pretreatment with tert-butylhydroquinone also increased survival of neuroblastoma cells in response to the three drugs tested [259]. Consistent with these findings, the role of Nrf2 in determining the efficacy of cisplatin was also demonstrated in ovarian cancer cells using small interfering RNA knockdown of Nrf2 [260]. Moreover, many Kelch-like ECH-associated protein 1 (Keap1) mutations or loss of heterozygosity in the Keap1 locus has been identified in lung cancer cell lines or cancer tissues [261,262]. Keap1 mutations or loss of heterozygosity resulted in inactivation of Keap1 or a reduced expression of Keap1, which up-regulated the protein level of Nrf2 and transactivation of its downstream genes [261,262]. Similar to Nrf2, the protective effect of heme oxygenase-1 (HMOX-1, or HO-1) in normal cells may protect from oxidative stress-related diseases. However, such an effect is undesirable in cancer because it provides a selective advantage for cancer cells to survive. Consistent with this notion, HMOX-1 has been found to be overexpressed in various tumor types. It is believed that overexpression of HMOX-1 facilitates cancer cell growth and survival in many ways, such as stimulating rapid growth of cancer cells, enhancing cancer cell resistance to stress and apoptosis, promoting angiogenesis of tumors, and aiding in metastasis of tumors [263]. In addition to HMOX-1, other Nrf2-downstream genes such as Prx1, GPx, and thioredoxin reductase were also up-regulated in many cancer cells or tissues and may contribute to chemoresistance [264–266]. In ovarian cancer, constitutive activation of ERK activity has been

associated with high tumorigenicity and chemoresistance [267,268]. In addition, functional analyses employing knockdown of MKP3, a member of the subfamily of protein tyrosine phosphatases known as dual-specificity phosphatases (MKPs) [269,270], and ectopic overexpression revealed the role of MKP3 in negatively regulating ERK1/2 activity and inhibiting tumorigenicity and chemoresistance in vitro and in vivo. MKP3 is capable of dephosphorylating ERK1/2 by protein–protein interactions via a mitogen-activated protein kinase interaction motif within the N-terminal ERK1/2-binding domain [271].

Radioresistance

Acquired tumor radioresistance can be induced during radiotherapy owing to tumor repopulation [272]. Although tumor radioresistance stands as a fundamental barrier limiting the effectiveness of radiation therapy, the exact molecular mechanisms underlying the radioadaptive response are largely unknown (Fig. 4). Olivieri et al. [273] first described an adaptive response of human lymphocytes to ionizing radiation. Since then, a substantial number of reports have made a strong case for the existence of cellular radioprotective mechanisms that can be activated in response to a small dose of ionizing radiation. It is assumed that a specific prosurvival signaling network is induced in irradiated mammalian cells.

The elevated basal NF-κB activity in certain cancers has been linked with tumor resistance to chemotherapy and radiation [274]. NF-κB in adaptive radioresistance is evidenced in mouse epidermal cells [275] and human keratinocytes, and inhibition of NF-κB blocks the adaptive radioresistance [275]. Human breast cancer cells treated with fractional γ-irradiation show an enhanced clonogenic survival and NF-κB activation [276,277]. Blocking NF-κB inhibited the adaptive radioresistance. These results provide the first evidence that activation of NF-κB is required for signaling the radioadaptive resistance by exposure to radiation. Together with the assumption that NF-κB is able to regulate more than 150 effector genes, these results suggest that NF-κB plays a key role in tumor radioadaptive resistance under fractional ionizing radiation. Furthermore, in a study [278] that immunocytochemically examined the levels of activated NF-κB protein in pretreatment cancer specimens and in resected specimens of patients with chemoradiotherapy resistance, the cancers expressed higher levels of cytoplasmic NF-κB than did the adjacent nonmalignant mucosa. Furthermore, Sandur et al. suggest that transient inducible NF-κB activation provides a prosurvival response to radiation that may account for the development of radioresistance [279].

On the other hand, hypoxia is a principal signature of the tumor microenvironment and is considered the most important cause of clinical radioresistance and local treatment failure. The response of cells to ionizing radiation is strongly dependent upon oxygen, which is traditionally explained by the “oxygen fixation hypothesis” [280]. Oxygen is so far the best radiosensitizer. De Ridder et al. demonstrated that iNOS, activated by proinflammatory cytokines, can radiosensitize tumor cells through endogenous production of NO [280]. They further observed that this radiosensitizing effect is transcriptionally controlled by hypoxia and by NF-κB. Consistently, NF-κB inhibition has been used as an approach to radiosensitize tumor cells, aiming at stimulating apoptosis and inhibiting DNA repair. Moreover, the inflammatory mediators TNF-α and NO have been repeatedly used as targets to radiosensitize tumor cells [281–285].

Stem cell survival

Cancer stem cells (CSCs) are cancer cells that have the ability to generate tumors through the processes of self-renewal and differentiation into multiple cells. Such cells persist in tumors as a distinct population and cause relapse and metastasis by giving rise to new tumors. The existence of CSCs may have several implications in cancer treatment, including disease identification, selection of drug targets, prevention of metastasis, and development of new intervention strategies.

The first conclusive evidence for CSCs was published in 1997 [286], and to date CSCs have been isolated from both leukemias and a variety of solid tumors, including breast, brain, pancreatic, prostrate, ovary, and colon cancers [287–293]. The pathways that regulate self-renewal of CSCs include wint (Wnt), Notch, Hedgehog, and tumor-suppressor genes such as PTEN and tumor protein 53 [294]. Although redox balance plays an important role in the maintenance of stem cell self-renewal and in differentiation, redox status in CSCs has yet to be explored. However, given the similarity between normal stem cells and CSCs and the fact that redox status plays an important role in cancer cell development, it is tempting to speculate that redox status may have a role in CSC survival. A recent study by Diehn et al. demonstrated that, similar to normal stem cells, subsets of CSCs in human and murine breast tumors have lower ROS levels than do the corresponding nontumorigenic cells [295]. The group further showed that lower levels of ROS were associated with increased free radical scavenging systems and that pharmacologic depletion of these scavengers significantly decreased clonogenicity and resulted in radiosensitization of CSCs. Additionally, two studies showed that

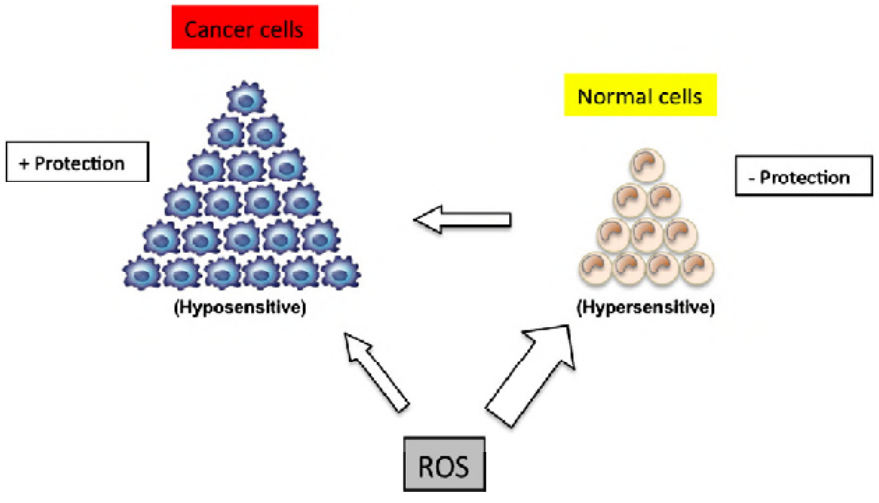

Fig. 4. Model of the sensitivity of normal cells versus cancer cells to reactive oxygen species. Normal cells are hypersensitive to ROS if not adequately protected by antioxidant mechanisms, which may lead to cancer formation. Cancer cells, on the other hand, have up-regulated antioxidant mechanisms (glutathione, SOD, catalase, and others) that will protect them against ROS, as can be observed in, for example, the case of radioresistance.

$CD133^+$ CSCs conferred chemoresistance to cisplatin and doxorubicin (known ROS generators) in ovarian cancer cells [296] and hepatocellular carcinoma [297], respectively. These studies further indicate that redox status may be important in maintaining CSC survival.

Stromal cell signaling

Cancer progression must involve both genetic and behavioral changes in cancer cells, and these changes are in part driven by the cancer-associated stromal cells and tumor microenvironment [298,299]. The stromal component of the normal prostate epithelium, for example, consists of smooth muscle, fibroblasts, vascular endothelial cells, nerve cells, inflammatory cells, insoluble matrix, and soluble factors [300]. Studies by De Marzo et al. highlight the role of inflammation in prostate cancer, suggesting that atrophic lesions are an early event in prostate carcinogenesis [301]. The macrophages in the tumor microenvironment produce ROS and RNS. The resulting increases in superoxide, hydrogen peroxide, hydroxyl radical, and free iron damage DNA, causing genetic mutations and initiating cancer progression. Tissue and cell recombination studies demonstrate the important regulatory role of fibromuscular stroma and stromal fibroblasts in prostate development and prostate carcinogenesis [300]. Cancer cells and stromal cells interact through physical contact or through soluble factors or insoluble extracellular matrix factors. These stromal fibroblasts, which interact with cancer cells, have increased levels of brain-derived neurotropic factor, chemokines, CC chemokine ligand 5 and CXC chemokine lix 5, versican, tenascin, connective tissue growth factor, stromal cell-derived factor-1/CXC chemokine ligand 12, and HIF-1α [302]. Other studies have demonstrated a role for stromal soluble factors interacting with receptors on prostate cancer cells. The stromal factors include VEGF, basic FGF, hepatocyte growth factor/scatter factor, transforming growth factor-β (TGF-β), insulin-like growth factor-1, IL-6, and keratinocyte growth factor [303].

Several studies have found that tumors promote a constant influx of myelomonocytic cells that express inflammatory mediators supporting protumoral functions. Myelomonocytic cells are key orchestrators of cancer-related inflammation associated with proliferation and survival of malignant cells, subversion of adaptive immune response, angiogenesis, stroma remodeling, and metastasis formation [304].

Tumor-derived factors, which cause sustained myelopoiesis, accumulation, and functional differentiation of myelomonocytic cells, provide an essential support for the angiogenesis and the stroma remodeling required for tumor growth [305,306]. In addition, it has long been known that tumor growth is promoted by tumor-associated macrophages (TAMs), a major leukocyte population present in tumors [65,307–310]. Accordingly, in many but not all human tumors, a high frequency of infiltrating TAMs is associated with poor prognosis. A model by which macrophages promote tumor invasion and metastasis includes expression of their proteolytic activity and subsequent breakdown of the basement membrane around the preinvasive tumors, thereby enhancing the ability of tumor cells to escape into the surrounding stroma [311]. In lung cancer, for example, TAMs may favor tumor progression by contributing to stroma formation and angiogenesis through their release of platelet-derived growth factor, in conjunction with TGF-β production by cancer cells [310]. TAMs produce several MMPs, such as MMP-2 and MMP-9, that degrade proteins in the extracellular matrix and also produce activators of MMPs, such as chemokines.

Conclusion

This review clearly implicates the role of ROS in various phases of tumorigenesis. Therefore, targeting redox-sensitive pathways and transcription factors offers great promise for cancer prevention and therapy. Numerous agents that can interfere with redox cell signaling pathways have been identified [9,312,313]. These include nutraceuticals derived from fruits, vegetables, spices, grains, and cereals. They have been shown to suppress tumorigenesis in preclinical models. Whether these agents can inhibit tumor growth in patients remains to be elucidated.

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